REMARKS

Reconsideration of the pending application is respectfully requested in view of the following remarks.

Status of the Application

Claims 1-64 are pending. Applicants have not introduced any amendments into the application.

Summary of the Office Action

Claims 1-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-47 of copending U.S. Patent Application No. 10/434,776. Claims 1-64 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent 6,399,087 ("Zhang") in view of U.S. Patent 6,576,245 ("Lundgren").

Discussion

At the outset, and in connection with the obviousness-type double patenting rejection, Applicants will file a terminal disclaimer after an indication of allowable subject matter is received.

Turing to the substantive rejection, Applicants respectfully traverse the obviousness rejection.

Zhang discloses and teaches compositions containing propofol—without more. Indeed, the sole focus of Zhang is teaching the preparation of an optimized propofol formulation that is bacteriostatic or fungistatic. Zhang purportedly solves this problem by providing a formulation containing relatively low amounts of lecithin and soybean oil.

In contrast to the claimed invention, Zhang does not even disclose, let alone provide any teaching relevant to, a container for its propofol compositions. Zhang, in fact, does not even mention a container. Because of this deficiency, Zhang cannot provide any teaching relative to which materials that may be useful in containers for propofol compositions, or provide any recognition that any part of a container may be the source of any problem with a

propofol composition. The law is well settled that the absence of such recognition alone is fatal to an obviousness rejection.

The Office Action recognizes this deficiency, and argues that it is cured by the combination of Zhang and Lundgren. According to the Office Action, Lundgren discloses low molecular weight peptide-based thrombin inhibitor in a primary package sealed with a rubber stopper or plunger containing bromobutyl rubber. The Office Action states that the combination of the references is proper because "bromobutyl rubber would inherently work for a low molecular weight (1,000 M.W.) composition such as propofol (M.W. 178.28)." *See Office Action, p. 5.*

Applicants respectfully submit that this argument is deficient in several respects. At the outset, Lundgren is not analogous because it is directed to solving the problem of degradation of certain peptide-based thrombin inhibitors, purportedly by using a rubber stopper or plunger containing bromobutyl rubber (and not chlorobutyl rubber). This is in marked contrast to Zhang which is directed not to solving the problem of peptide degradation, but to reducing microbial growth in propofol compositions. As the components (peptide-based thrombin inhibitors, propofol compositions) and problems (degradation of specific peptide-based thrombin inhibitors, microbial growth in propofol composition) facing Lundgren are not the same as that those facing Zhang, one skilled in the art would not only fail to look to Lundgren for a solution, but would not be motivated to use the Lundgren stopper in connection with a Zhang propofol composition because the latter does not contain one of the Lundgren peptide-based thrombin inhibitors, and Zhang fails to recognize that any problem with its propofol composition is attributable to a container. Indeed, one skilled in the art reading Zhang would be motivated only to further reduce the amount of solvent therein.

In addition, Applicants submit that the teaching attributable to Lundgren in the Office Action is not fairly based on the actual language of the reference. A fair reading of the reference by one skilled in the art is that Lundgren solves a problem associated with only those peptide-based thrombin inhibitors disclosed therein. Indeed, there is nothing in Lundgren that suggests that its solution is universally applicable to actives other than those specifically disclosed therein, let alone to the specific propofol compositions disclosed in

Zhang. Indeed, there is no mention of propofol compositions in Lundgren at all. The only basis for the combination is improper hindsight.

Even if one were to assume *arguendo* the asserted combination was proper, however, the combination would not provide the invention as claimed.

Lundgren teaches that bromobutyl rubber closures prevent degradation of peptide-based thrombin inhibitors, whereas chlorobutyl rubber closures do not. In contrast, Example 33 of the instant application demonstrates a discovery by Applicants that not all bromobutyl rubber closures prevented degradation of propofol compositions. In fact, different types of bromobutyl rubbers (i.e., Rubbers 1, 2, and 3) had varying effects (52.9%, 93.4%, and 99.9% propofol percentage of control, respectively,) on propofol compositions containing 3% by weight soybean oil. In addition, whereas Lundgren discloses that chlorobutyl rubber closures did not prevent degradation of thrombin inhibitors, Example 33 shows that chlorobutyl rubber closures (Rubber 4) resulted in a 95.8% propofol concentration, that is, only a 4.2% loss of propofol compared to control. Thus, not only are the teachings of Lundgren inapplicable to propofol compositions (for the reasons set forth above), the asserted combination would not yield the invention as claimed.

Further, there is absolutely no recognition in either of the cited references that degradation or potency loss of a propofol composition could occur even if the weight percent of solvent used in such a composition was relatively low, or that the type of closure material would have an effect on the degradation or potency loss of such propofol compositions. For example, and as shown in Examples 32-37 of the instant application, propofol compositions containing relatively low amounts of solvent, e.g., less than 10% by weight of solvent (e.g., soybean oil), degraded to a greater extent when contacted with certain closure materials, whereas propofol compositions containing at least 10% by weight of solvent did not. As neither Zhang nor Lundgren recognizes the foregoing, neither motivates one skilled in the art to provide the invention as claimed, e.g., a sterile pharmaceutical composition for parenteral administration of propofol, said composition comprising propofol, and less than about 10% by weight solvent for propofol, wherein said composition is stored in a container having a closure wherein said closure is inert to propofol (claim 1).

In view of the foregoing, Applicants respectfully request that the obviousness rejection be withdrawn.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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Date: November 16, 2006